

Claims:-

- Sub B₁ 1. A method of making microparticles of a sustained release ionic conjugate containing a free carboxyl group-containing biodegradable polymer and a free amino group-containing drug which are ionically bonded to each other, the method comprising:

5 obtaining a first solution in which said conjugate is dissolved, wherein said solution comprises acetone, acetonitrile, ethyl acetate, tetrahydrofuran, or glyme; 112

10 mixing said first solution with a first liquid to form a first dispersion, wherein said first liquid is miscible with said first solution, and said conjugate is not soluble in said first liquid and precipitates out of said first dispersion; and

isolating said conjugate from said first dispersion.

- 15 2. A method according to claim 1, wherein said first solution is added to said first liquid as small droplets.

3. A method according to claim 2, wherein said first solution is added to said first liquid through an atomizing nozzle.

4. A method according to Claim 1 any one of claims 1-3, wherein said drug is a peptide.

20 5. A method according to Claim 1 any preceding claim, wherein said biodegradable polymer is a polyester made of lactic acid, e-caprolic acid, glycolic acid, trimethylene carbonate, or p-dioxanone; or a copolymer thereof.

25 6. A method according to Claim 1 any preceding claim, wherein said drug is soluble in said first liquid.

09171740-042099

B

SF7666

A+B
✓
1st sol'n

acetone
Non-solvent!

Claim 1
 7. A method according to ~~any preceding claim~~, wherein said biodegradable polymer is a polyester comprising lactic acid, or glycolic acid; or a copolymer thereof.

5 *SFTGCU* → 8. A method according to claim 7, wherein said polyester further contains malic acid, tartaric acid, citric acid, succinic acid, or glutaric acid. *1 OH diff.*

9. A method according to ~~any one of claims 4-8~~, wherein said peptide is a somatostatin or LHRH. *Claim 4 2 OH diff.*

10 *X* 10. A method according to ~~any preceding claim~~, wherein said first liquid is alcohol or water; or a mixture thereof. *Claim 1*

X 11. A method according to claim 10, wherein said first liquid is ethanol maintained between about 0°C and -30°C or isopropyl alcohol maintained between about 0°C and -70°C.

15 12. A method according to ~~any preceding claim~~, wherein said first solution contains acetone or acetonitrile. *Claim 1*

13. A method according to ~~any preceding claim~~, wherein said first solution is obtained by:

dissolving said biodegradable polymer in a second liquid to form a second solution;

20 dissolving said drug in a third liquid to form a third solution, wherein said third liquid is miscible with said first liquid and said second liquid; and

25 *A sol'n + B sol'n*
↓
1st sol'n
 mixing said second solution and said third solution to form said first solution, wherein said mixing causes said drug to ionically bond to said biodegradable polymer and form said conjugate in said first solution.

14. A method according to claim 13, wherein NaOH or KOH is added to the second solution prior to mixing said second solution and said third solution.

5 15. A method according to claim 13 ~~or 14~~, wherein said second liquid is acetone; and said third liquid is water or acetone; or a mixture thereof.

10 16. A method according to ~~any of claims 1-12~~, wherein said first solution is obtained by dissolving said biodegradable polymer and said drug in a second liquid to form said first solution, thereby forming said conjugate in said first solution.

17. A method according to claim 16, wherein said second liquid is acetone or a mixture of acetone and water.

15 18. A method according to claim 17, wherein said biodegradable polymer is first dissolved in said second liquid, a base is then added to said second solution, and said drug is subsequently dissolved in said second liquid.

19. A method according to ~~any preceding claim~~, wherein said conjugate is isolated by centrifuging or filtering said first dispersion.

20 20. A method according to claim 19, wherein said first solution is partially or completely evaporated from said first dispersion prior to isolation of said conjugate.

~~21. A method according to claim 20, wherein said isolated conjugate is mixed with an aqueous mannitol solution prior to vacuum drying.~~

25 ~~22. A method of spherifying a sustained release ionic conjugate comprising a biodegradable polymer containing a free carboxyl group-containing biodegradable polymer and a free amino group-containing drug which are ionically bonded to each other, said method comprising:~~

mixing said conjugate with a first liquid to form a first dispersion, wherein said conjugate has the shape of a microparticle and is not soluble in said first liquid;

5 heating said first dispersion to a temperature greater than the T_g or T_m of said conjugate;

cooling said first dispersion below the T_g or T_m of said conjugate;

10 mixing said first dispersion with a second liquid to form a second dispersion, wherein said second liquid is miscible with said first liquid and said conjugate is not soluble in said second liquid; and

isolating said conjugate from said second dispersion.

15 23. A method according to claim 22, wherein said conjugate has the shape of a microcapsule which has an average diameter of between 5 μ m to 200 μ m prior to mixing with said first liquid and said first dispersion is stirred prior to said heating or cooling.

24. A method according to claim 22 ~~or 23~~, wherein said biodegradable polymer is a polyester made of lactic acid or glycolic acid; or a copolymer thereof.

20 25. A method according to *Claim 22* ~~any one of claims 22-24~~, wherein said drug is a peptide.

26. A method according to *Claim 22* ~~any one of claims 22-25~~, wherein said first liquid is an oil and said second liquid is hexane.

27. A method according to *Claim 22* ~~any one of claims 22-26~~, further comprising:

25 rinsing said isolated conjugate with said second liquid; and

vacuum drying said rinsed conjugate.

28. A method according to claim 27, wherein said isolated conjugate is mixed with an aqueous mannitol solution prior to vacuum drying.

5 ~~28.~~ 29. A method of spherifying a sustained release ionic conjugate containing a free carboxyl group-containing biodegradable polymer and a free amino group-containing drug which are ionically bonded to each other, said method comprising:

dissolving said conjugate in a first liquid to form a first solution;

10 stirring said first solution with a second liquid to form a first dispersion, wherein said second liquid is immiscible with said first solution;

evaporating said first liquid from said first dispersion to precipitate said conjugate from said first dispersion; and

15 isolating said precipitate conjugate from said first dispersion.

30. A method according to claim 29, wherein said first solution is added to said second liquid as small droplets.

31. A method according to claim 29 ~~or 30~~, wherein said first liquid is acetonitrile and said second liquid is an oil.

20 32. A method according to claim 31, wherein said oil is silicon oil, mineral oil, sesame oil, or a vegetable oil.

Claim 29
33. A method according to ~~any one of claims 29-32~~, wherein said biodegradable polymer is a polyester comprising lactic acid or glycolic acid; or a copolymer thereof.

Claim 29

34. A method according to ~~any one of claims 29-33~~, wherein said drug is a peptide.

Claim 29

5 35. A method according to ~~any one of claims 29-34~~, further comprising rinsing said isolated conjugate with a third liquid which is miscible with said second liquid and not a solvent for said isolated conjugate.

36. A method according to claim 35, wherein said third liquid is hexane, heptane, or octane.

Claim 29

10 37. A method according to ~~any one of claims 29-36~~, wherein said isolated conjugate is mixed with an aqueous mannitol solution prior to vacuum drying.

38. A method of making microparticles of a sustained release ionic conjugate, substantially as hereinbefore described and exemplified.

15 39. A method of spherifying a sustained release ionic conjugate, substantially as hereinbefore described and exemplified.

660240-0427260

- 23 -

1 40. A method according to claim 8, wherein said
2 polyester comprises lactic acid, glycolic acid and tartaric
3 acid.

Table V Analis

1 ~~41.~~ Biodegradable polymer comprising lactic acid, ϵ -
2 caproic acid, glycolic acid, trimethylene carbonate, p-
3 dioxanone or a copolymer thereof and tartaric acid.

1 42. Microparticles comprising a biodegradable polymer
2 according to claim 41.

1 43. Microparticles of a sustained release ionic
2 conjugate comprising the biodegradable polymer according to
3 claim 41 and a drug containing one or more free amino groups,
4 wherein the polymer and drug are ionically bonded.

1 44. Microparticles according to claim 43 wherein said
2 drug is selected from the group consisting of growth hormone
3 releasing peptide luteinizing hormone-releasing hormone,
4 adrenomedullin, growth hormone, somatostatin, bombesin,
5 gastrin releasing peptide, calcitonin, bradykinin, galanin,
6 melanocyte stimulating hormone, growth hormone releasing
7 factor, amylin, tachykinins, secretin, parathyroid hormone,
8 enkephalin, endothelin, calcitonin gene releasing peptide,
9 neuromedins, parathyroid hormone related protein, glucagon,
10 neurotensin, adrenocorticotrophic hormone, peptide YY,
11 glucagon releasing peptide, vasoactive intestinal peptide,
12 pituitary adenylated cyclase activating peptide, motilin,
13 substance P, neuropeptide Y and TSH or an analogue or a
14 fragment thereof.

1 45. Microparticles according to claim 44 wherein said
2 drug is somatostatin or LHRH or an analogue or a fragment
3 thereof.

660240" 0727260

1 46. Microparticles according to claim 45 wherein said
2 somatostatin analogue is D- β -Nal-c[Cys-Tyr-D-Trp-Val-Cys]-Thr-
3 NH₂.

1 47. The biodegradable polymer according to claim 41
2 comprising lactic acid glycolic acid and tartaric acid.

1 48. Microparticles comprising a biodegradable polymer
2 according to claim 47.

1 49. Microparticles of a sustained release ionic
2 conjugate comprising the biodegradable polymer according to
3 claim 47 and a drug containing one or more free amino groups,
4 wherein the polymer and drug are ionically bonded.

1 50. Microparticles according to claim 49 wherein said
2 drug is selected from the group consisting of growth hormone
3 releasing peptide, luteinizing hormone-releasing hormone,
4 adrenomedullin, growth hormone, somatostatin, bombesin,
5 gastrin releasing peptide, calcitonin, bradykinin, galanin,
6 melanocyte stimulating hormone, growth hormone releasing
7 factor, amylin, tachykinins, secretin, parathyroid hormone,
8 enkephalin, endothelin, calcitonin gene releasing peptide,
9 neuromedins, parathyroid hormone related protein, glucagon,
10 neurotensin, adrenocorticotrophic hormone, peptide YY,
11 glucagon releasing peptide, vasoactive intestinal peptide,
12 pituitary adenylated cyclase activating peptide, motilin,
13 substance P, neuropeptide Y and TSH or an analogue or a
14 fragment thereof.

1 51. Microparticles according to claim 50 wherein said
2 drug is somatostatin or LHRH or an analogue or a fragment
3 thereof.

1 52. Microparticles according to claim 51 wherein said
2 somatostatin analogue is D- β -Nal-c[Cys-Tyr-D-Trp-Val-Cys]-Thr-
3 NH₂.

1 53. The biodegradable polymer according to claim 47
2 wherein the ratio of lactic acid to glycolic acid to taratic
3 acid is about 66 to about 33 to about 1, respectively.

1 54. Microparticles comprising a biodegradable polymer
2 according to claim 53.

1 55. Microparticles of a sustained release ionic
2 conjugate comprising the biodegradable polymer according to
3 claim 53 and a drug containing one or more free amino groups,
4 wherein the polymer and drug are ionically bonded.

1 56. Microparticles according to claim 55 wherein said
2 drug is selected from the group consisting of growth hormone
3 releasing peptide, luteinizing hormone-releasing hormone,
4 adrenomedullin, growth hormone, somatostatin, bombesin,
5 gastrin releasing peptide, calcitonin, bradykinin, galanin,
6 melanocyte stimulating hormone, growth hormone releasing
7 factor, amylin, tachykinins, secretin, parathyroid hormone,
8 enkephalin, endothelin, calcitonin gene releasing peptide,
9 neuromedins, parathyroid hormone related protein, glucagon,
10 neurotensin, adrenocorticotrophic hormone, peptide YY,
11 glucagon releasing peptide, vasoactive intestinal peptide,
12 pituitary adenylated cyclase activating peptide, motilin,
13 substance P, neuropeptide Y and TSH or an analogue or a
14 fragment thereof.

1 57. Microparticles according to claim 56 wherein said
2 drug is somatostatin or LHRH or an analogue or a fragment
3 thereof.

1 58. Microparticles according to claim 57 wherein said
2 somatostatin analogue is D- β -Nal-c[Cys-Tyr-D-Trp-Val-Cys]-Thr-
3 NH₂.

1 59. The biodegradable polymer according to claim 47
2 wherein the ratio of lactic acid to glycolic acid to taratic
3 acid is about 66 to about 32 to about 2, respectively.

1 60. Microparticles comprising a biodegradable polymer
2 according to claim 59.

1 61. Microparticles of a sustained release ionic
2 conjugate comprising the biodegradable polymer according to
3 claim 60 and a drug containing one or more free amino groups,
4 wherein the polymer and drug are ionically bonded.

1 62. Microparticles according to claim 61 wherein said
2 drug is selected from the group consisting of growth hormone
3 releasing peptide, luteinizing hormone-releasing hormone,
4 adrenomedullin, growth hormone, somatostatin, bombesin,
5 gastrin releasing peptide, calcitonin, bradykinin, galanin,
6 melanocyte stimulating hormone, growth hormone releasing
7 factor, amylin, tachykinins, secretin, parathyroid hormone,
8 enkephalin, endothelin, calcitonin gene releasing peptide,
9 neuromedins, parathyroid hormone related protein, glucagon,
10 neurotensin, adrenocorticotrophic hormone, peptide YY,
11 glucagon releasing peptide, vasoactive intestinal peptide,
12 pituitary adenylated cyclase activating peptide, motilin,
13 substance P, neuropeptide Y and TSH or an analogue or a
14 fragment thereof.

1 63. Microparticles according to claim 62 wherein said
2 drug is somatostatin or LHRH or an analogue or a fragment
3 thereof.

1 64. Microparticles according to claim 63 wherein said
2 somatostatin analogue is D- β -Nal-c[Cys-Tyr-D-Trp-Val-Cys]-Thr-
3 NH₂.

1 65. A method according to claim 21 wherein said
2 polyester comprises lactic acid, glycolic acid and tartaric
3 acid.

1 66. A method according to claim 28 wherein said
2 polyester comprises lactic acid, glycolic acid and tartaric
3 acid.

1 67. A method according to claim 37 wherein said
2 polyester comprises lactic acid, glycolic acid and tartaric
3 acid.

09171740-042099